# Chapter 5
# Towards the Synthesis of Mycosides; Virulent Markers of Mycobacteria

*This chapter describes a new strategy for the construction of phenylphthiocerol, a substructure of Mycosides (phenolic glycolipids). Mycosides are outer membrane lipids of mycobacteria and play an important role in the virulence of mycobacteria. Hetero asymmetric allylic alkylation, cross-metathesis and Sharpless epoxidation reactions are key strategic elements in the synthesis towards phenylphthiocerol and eventually mycosides.**

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## 5.1 Introduction

Mycosides (phenolic glycolipids) are a class of outer membrane waxy lipids which are present in all pathogenic mycobacteria with the exception of *Mycobacterium gastri*. Mycosides typically consist of a long chain *p*-glycosylated, 3-methoxy, 4-methyl, 9,11-dihydroxy glycol (glycosyl phenolphthiocerol) containing scaffold di-esterified with di-, tri-, and tetra-methyl-branched acyl chains (mycocerosates, Chapter 2).[1] Mycoside B (Figure 1) is an example of a mycoside and is found in virulent *Mycobacterium bovis* (*M. bovis*). Phthiocerol dimycocerosate A (PDIM A, Figure 1), a closely related structure to mycosides, is found in virulent *Mycobacterium tuberculosis* (*M. tuberculosis*) and contains a phthiocerol backbone instead of the phenolphthiocerol.

The structure and absolute configuration of mycocerosic acid were proposed by Polgar and Smith in 1963.[2] We have recently reported the first catalytic asymmetric synthesis of mycocerosic acid and we have confirmed its structure and absolute configuration (Chapter 2).[3]

Phthiocerol was first reported by Anderson and Stodola in 1936[4] and the basic structure was elucidated by Stenhagen and co-workers[5] in 1956. The stereochemistry of phthiocerol and phenolphthiocerol has been studied extensively over the last decades.[6,7,8,9,10] More recent studies, involving MALDI-TOF and $^{1}$H-NMR analysis, support this overall structural assignment,[11] but rigorous confirmation by chemical synthesis was lacking.[12] We recently confirmed the stereochemistry and absolute configuration by reporting the first synthesis of PDIM A.[13]

Mycoside B is one of the lipids present in the cell envelope of *Mycobacterium bovis* (*M. bovis*), the causative agent of tuberculosis in cattle (known as bovine tuberculosis). Being related to *M. tuberculosis*, *M. bovis* can jump the species barrier and cause tuberculosis in humans.[14] The complete structure of Mycoside B was first described by Demarteau-Ginsburg and Lederer in 1963.[15]

It is noteworthy to mention that there are several anomalies in the stereochemistry of phenolphthiocerol and phthiocerol in some mycobacteria species. *Mycobacterium marinum* and *Mycobacterium ulcerans* produce phthiocerols that contain mycocerosic acid residues with the

opposite stereochemistry, all-*S*, compared to the more commonly found all-*R* configuration.[16] The 9,11-dihydroxy moiety (1,3-diol), which is typically found as the *R,R-threo* (*anti*) configuration, is only observed as the *erythro* or *syn*-diol in *M. marinum*. The absolute configuration of these *syn*-diols is still unknown. The C-4 methyl branch is also of the opposite configuration (*R*) compared to that in the other mycobacteria (*S*).[17] *M. marinum* and *M. ulcerans* do, however, differ at their C-3 center. *M. ulcerans* produces phthiocerols with a carbonyl functionality at the C-3 position compared to a hydroxy functionality (methoxy) in *M. marinum*.[17a]

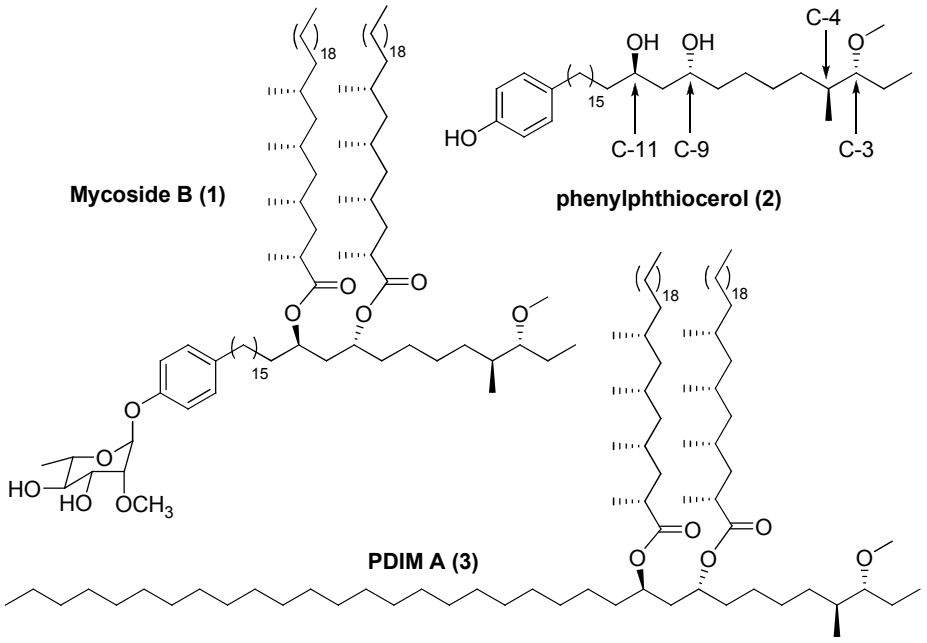
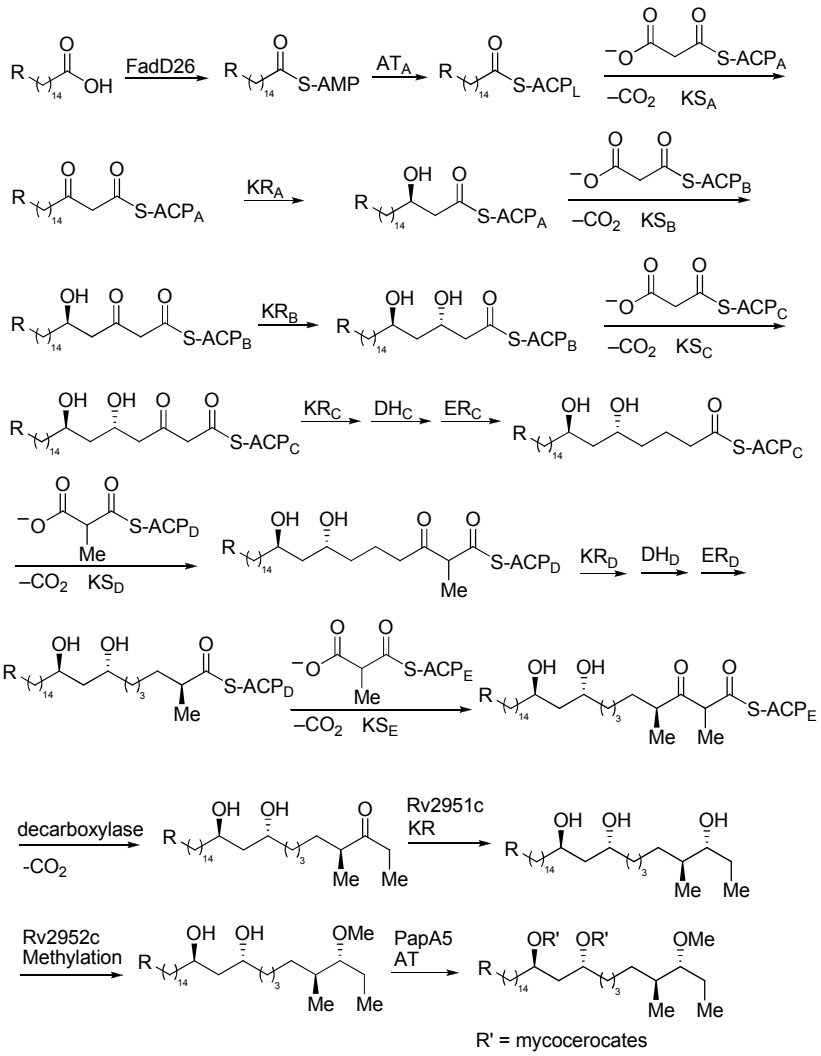



**Figure 1:** Molecular structures of phthiocerol containing PDIM A (*M. tuberculosis)* and phenylphthiocerol containing Mycoside B (*M. bovis*).

Until recently, little was known about the biosynthesis of (phenol)phthiocerol. Due to the availability of several mycobacterial genomes, at the moment tremendous progress is made toward clarifying their biosynthetic pathways.[18] This was recently extensively reviewed by Onwueme *et al.*[19] and new enzymes involved in the biosynthetic pathway

have been discovered.[20] The proposed general biosynthetic pathway for (phenol)phthiocerol is depicted in Scheme 1.[21]



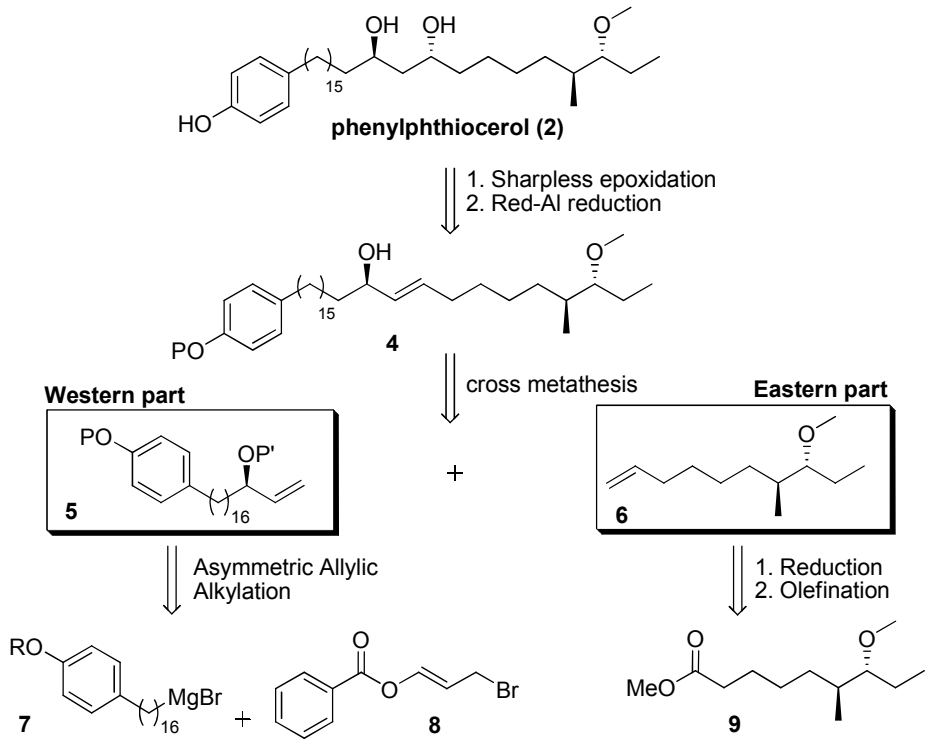

**Scheme 1:** Biosynthetic pathway for DIMs, R = $CH_3(CH_2)_{5\text{-}7}CH$- or $HOPhCH_2CH_2$-, AT = acyltransferase, KS = keto-acyl synthase, KR = ketoreductase, DH = dehydratase, ER = enoyl reductase.

After we successfully synthesized PDIM A (synthesis of phthiocerol by Dr. Eva Casas Arce)[22] we decided to embark on the first asymmetric synthesis

of the related, but considerably more complex phenolphthiocerol based Mycoside B (Figure 1, **1**), starting with the synthesis of phenylphthiocerol (**2**).

## 5.2 Retrosynthetic analysis of phenylphthiocerol

As outlined in the retrosynthetic scheme (Scheme 2), we were interested in a new strategy for the efficient construction of the *anti*-1,3 diol unit which is present in phenylphthiocerol. We planned to use a Sharpless epoxidation[23] on **4** followed by reductive opening of the resulting epoxide[24] to obtain the desired anti-1,3 diol structure in **2**. In order to synthesize allylic alcohol **4**, a cross coupling metathesis of building blocks **5** and **6** was envisioned.[25] The key step for the formation of allylic alcohol **5** would be the hetero asymmetric allylic alkylation of **8** using alkylmagnesium bromide **7**.[26] On the other hand, building block **6** could be obtained by a reduction, olefination sequence of methyl ester **9**.[13]

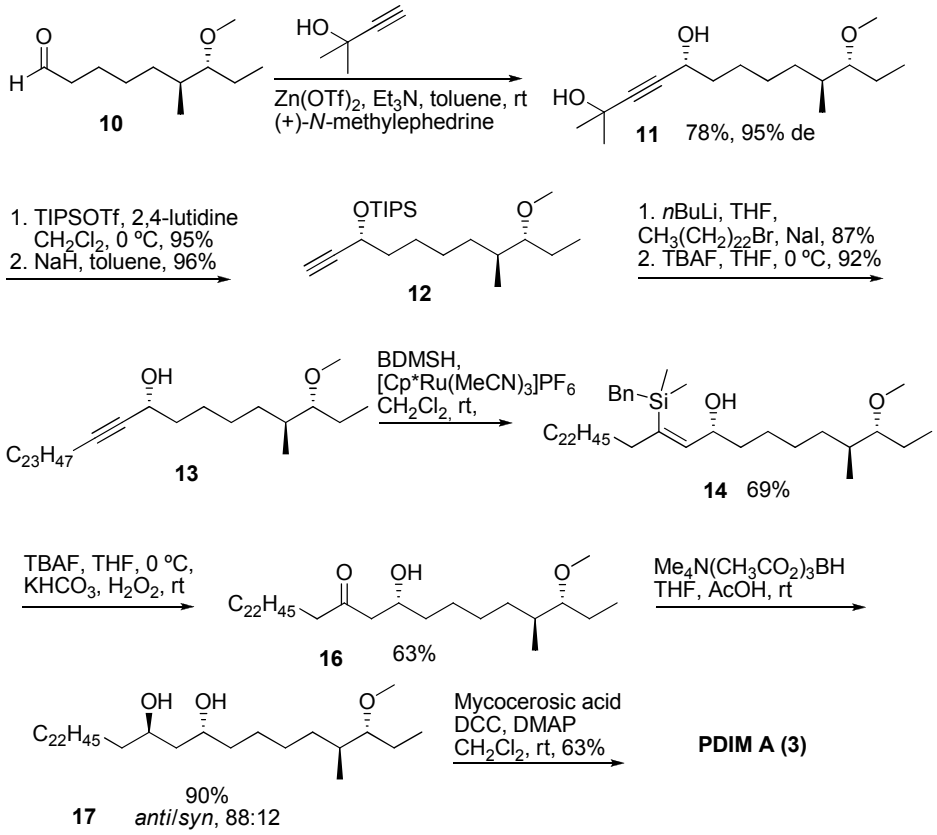



**Scheme 2:** Retrosynthetic analysis of phenylphthiocerol (**2**)

## 5.3 Synthesis of PDIM A

In 2006 we reported the first total synthesis of PDIM A. Enantioselective addition of 2-methyl-3-butyn-2-ol to aldehyde **10** in the presence of $Zn(OTf)_2$, $Et_3N$, and (+)-*N*-methylephedrine[27] allowed for the formation of propargylic alcohol **11** (Scheme 3) with excellent selectivity (95% de).[28] The hydroxy group in **11** was protected as a silyl ether, and the alkyne moiety was deprotected under basic conditions to afford **12**. Alkylation of the corresponding alkynyllithium compound using $CH_3(CH_2)_{22}Br$ in the presence of NaI afforded the protected propargylic alcohol.[29] Finally, treatment with tetrabutylammonium fluoride (TBAF) led to the formation of deprotected alcohol **13**. We were pleased to observe regioselective hydrosilylation of propargylic alcohol **13** with benzyldimethylsilane

(BDMSH) catalyzed by $[Cp^*Ru(MeCN)_3]PF_6$, following the protocol described by Trost.[30]




**Scheme 3:** Key steps in the synthesis of PDIM A.

This reaction represents a versatile method in natural product synthesis.[30,31] It afforded a mixture of benzyldimethyl silanes (4:1) favoring **14** (69% yield). Fleming-Tamao oxidation,[32] using TBAF, $KHCO_3$ and $H_2O_2$, resulted in the formation of the corresponding hydroxy ketones, which could be separated by column chromatography affording **16** as a pure isomer. To selectively produce the *anti*-1,3-diol, reduction of **16** was carried out with tetramethylammonium triacetoxyborohydride, resulting in **17** with an *anti*/*syn* ratio of 88:12.[33] Double esterification of phthiocerol

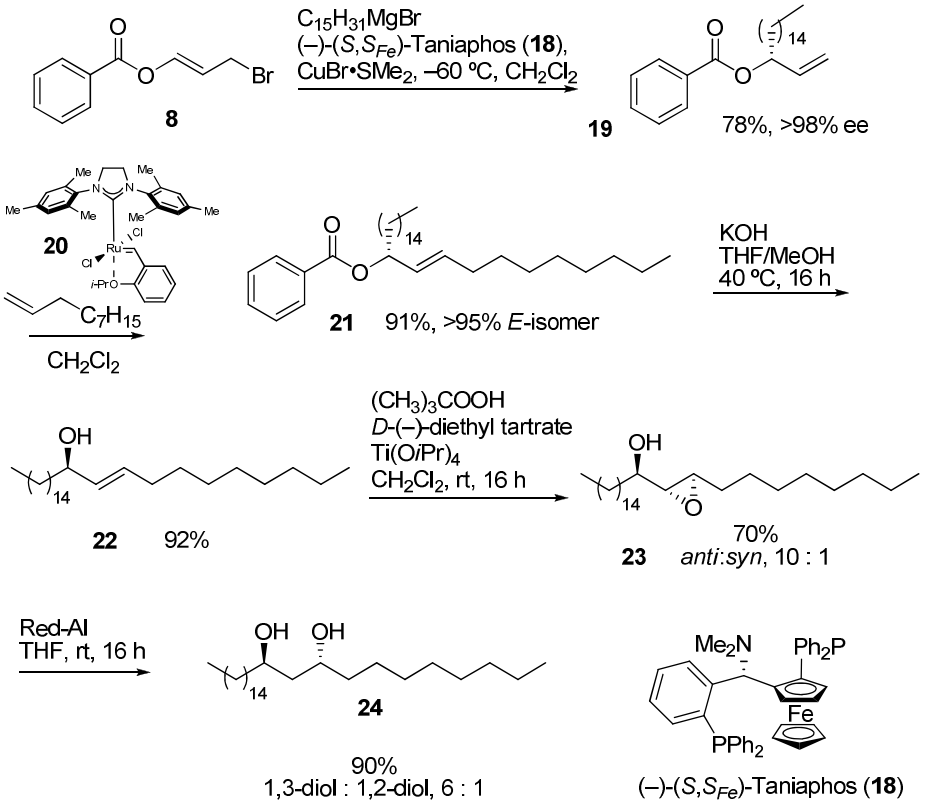
with mycocerosic acid gave PDIM A (**3**) in 63% yield (15 steps and 5.6% overall yield) (Scheme 4).[34]

Although this synthesis is very elegant and it demonstrates the power of state of the art catalytic protocols, we were interested to find a shorter route for the construction of the *anti*-1,3-diol motif. Therefore, we were interested in constructing the 1,3-diol motif of phenolphthiocerol by applying our earlier developed hetereo asymmetric allylic alkylation reaction combined with cross-metathesis and Sharpless epoxidation reactions (Section 5.2).

## 5.4 Results and discussion

### 5.4.1 New enantioselective approach for the construction of 1,3-diols

In order to guarantee the success of the newly designed route for the construction of the *anti* 1,3-diol motif, the key steps were first studied on model substrates (Scheme 4). Thus, commercially available *n*-pentadecylmagnesium bromide and dec-1-ene were used instead of Grignard **7** and alkene **6**, respectively. Copper/Taniaphos (**18**) catalyzed hetero asymmetric allylic alkylation of **8**[26,35] using *n*-pentadecylmagnesium bromide led to the formation of allylic ester **19** with 78% yield and >98% ee. Cross coupling metathesis with dec-1-ene using Hoveyda-Grubbs 2$^{nd}$ generation catalyst **20** allowed the formation of **21** with excellent yield and selectivity (91% yield, >95% *E* isomer).[36] Treatment of **21** under basic conditions led to the formation of allylic alcohol **22**, which was submitted to a Sharpless epoxidation resulting in the formation of **23** as mixture of *anti*:*syn* epoxides (10:1), easily separable by column chromatography.




**Scheme 4:** Model study on the enantioselective construction of the *anti* 1,3-diol

Starting with the *R*-enantiomer of allylic alcohol **22**, *si*-face attack on olefin **22** directed by the titanium *D*-(–)-diethyl tartrate complex resulted in the desired *R*,*R*,*R*-**23** epoxide (Figure 2).

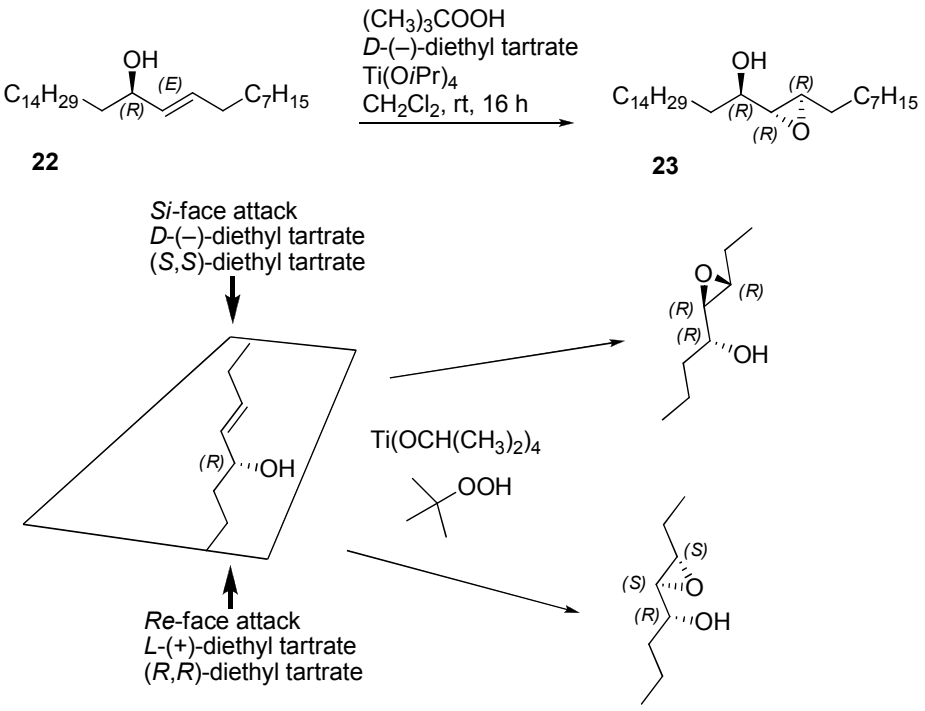


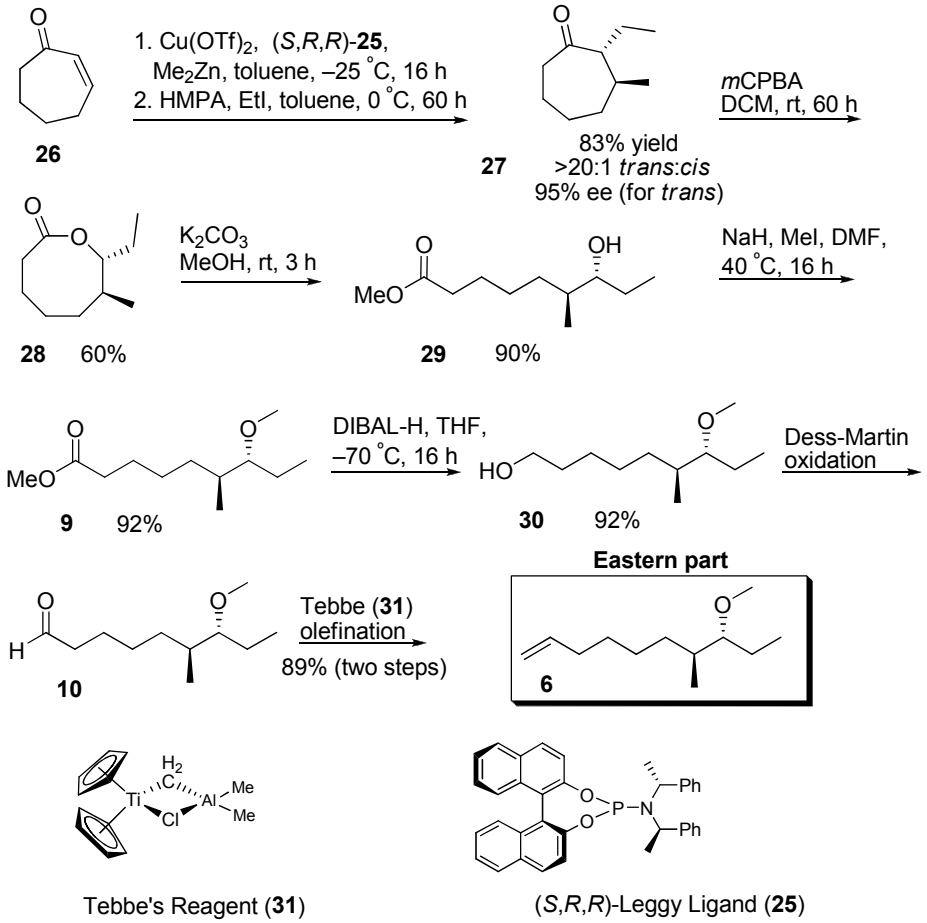

**Figure 2:** Stereoselectivity in the Sharpless epoxidation reaction.

Finally, reductive opening of *anti*-**23** using Red-Al completed the synthesis of model substrate **24**. The selectivity of the reductive epoxide opening was highly dependent on the temperature.[37] Reaction temperatures of –20 and 0 °C resulted in 1:1 and 1:2 mixtures, respectively, favoring the desired 1,3-diol. At room temperature the selectivity improved to 1:6.

### 5.4.2 Synthesis of the Eastern part of phenylphthiocerol

Olefin **6** was prepared from aldehyde **10**, following the protocol we recently disclosed (Scheme 5).[13] Copper/phosphoramidite (**25**) catalyzed asymmetric conjugate addition of $Me_2Zn$ to cycloheptenone (**26**), followed by *in situ* ethylation allowed the formation of ketone **27**, which was isolated in high yield and with excellent trans selectivity (>20:1) and ee (95%). Baeyer-Villiger oxidation using excess *m*CPBA followed by treatment of the resulting lactone **28** with $K_2CO_3$ in MeOH led to the formation of the

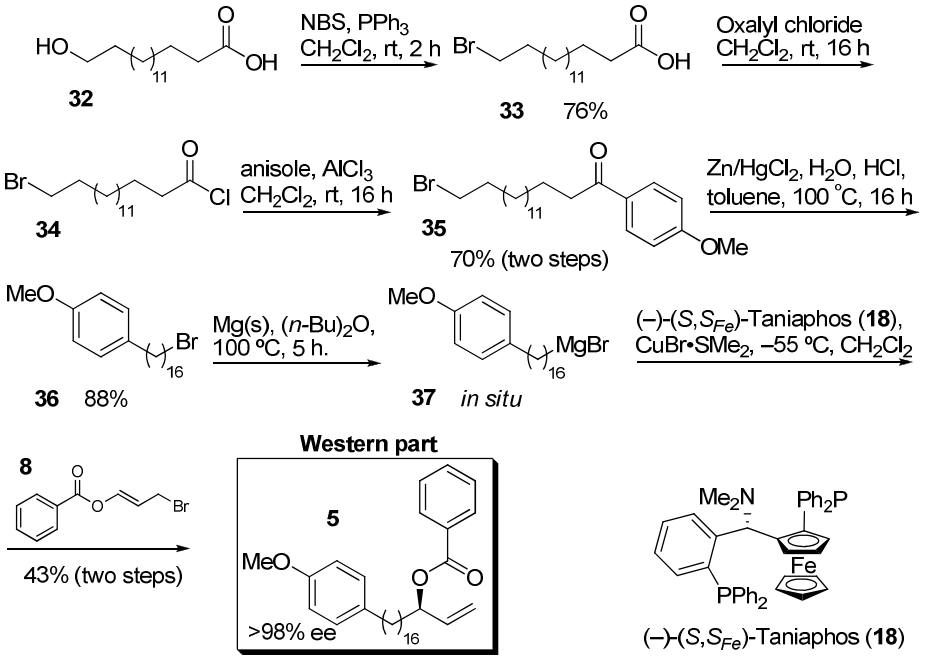
linear methyl ester **29**. The hydroxyl group of **29** was converted into its methyl ether **9** after which the ester moiety was reduced to the corresponding alcohol **30**. Following this protocol, 500 mg of alcohol **30** was prepared.[38] To complete the synthesis of olefin **6**, alcohol **30** was oxidized to aldehyde **10** using Dess-Martin reagent. Aldehyde **10** was directly treated with Tebbe's olefination reagent (**31**) and olefin **6** was obtained in 89% yield over the last two steps.




**Scheme 5:** Synthesis of the Eastern part of phenylphthiocerol.

### 5.4.3 Synthesis of the Western part of phenylphthiocerol

The construction the Western part **5** (Scheme 6) started with the substitution of the hydroxyl group in 16-hydroxyhexadecanoic acid (**32**) to bromo-derivative **33**, followed by formation of the corresponding acyl chloride **34**. Friedel-Craft acylation of anisole using **34** led to ketone **35**, which was reduced under Clemmensen conditions to complete the synthesis of bromo-derivative **36**.[39]




**Scheme 6:** Synthesis of the Western part of phenylphthiocerol.

Formation of the Grignard reagent from bromo-derivative **36** was found to be surprisingly difficult under standard conditions in diethyl ether. Although we managed to observe the formation of the alkyl magnesium species in some cases, in most attempts the starting material was recovered. Bromide **36** was found to be more reactive in refluxing THF and the formed Grignard reagent was more soluble. However, because of the strong

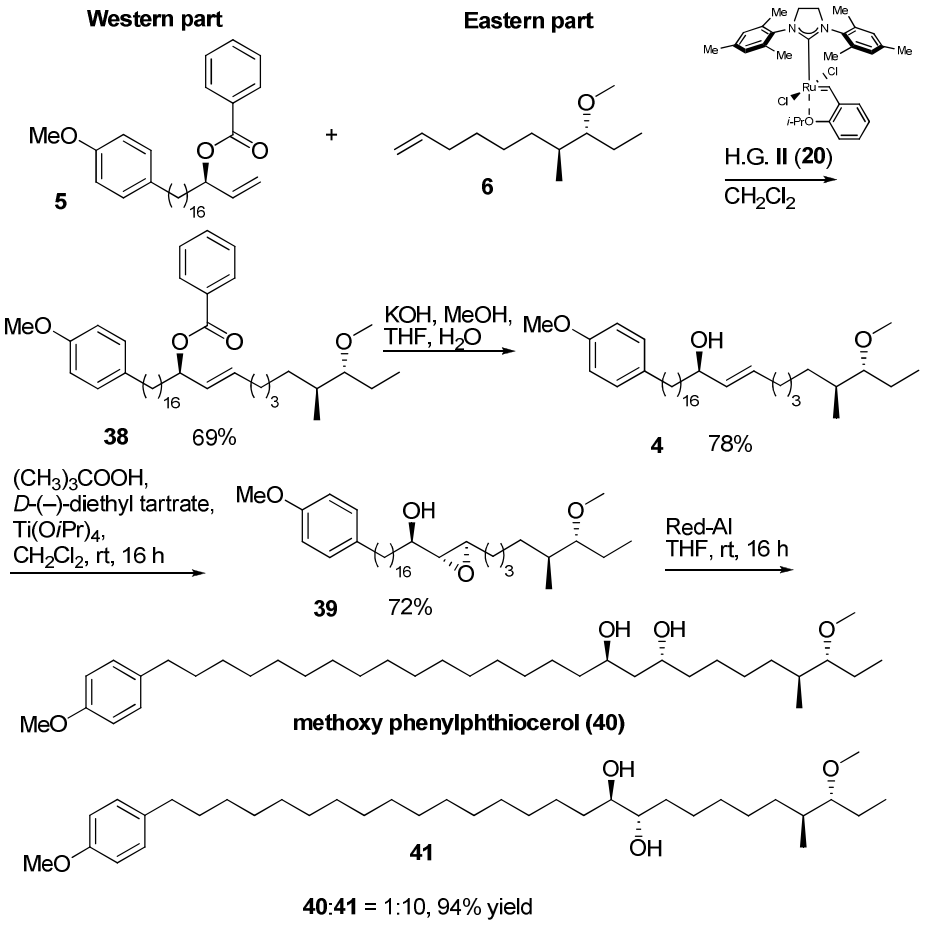
coordinating character (Lewis base) of THF, there is a strong competition between the chiral ligand and the solvent with the copper-catalyst. THF mostly prohibits the enantioselectivity of the asymmetric enantioselective allylic alkylation reaction as well as the enantioselectivity in the enantioselective 1,4-addition reactions.[40] Attempts to perform a solvent exchange by evaporating the THF followed by the addition of diethyl ether were unsatisfactory. The solid Grignard reagent was difficult to dissolve in diethyl ether and the presence of THF could not be ruled out. We therefore decided to use a di-alkyl ether with a higher boiling point compared to diethyl ether so we would have higher reactivity with similar polarity and coordinating character as diethyl ether. Switching to di-*n*-butyl ether at 100 °C for 5 h resulted in the desired formation of Grignard reagent **37**! The *n*-butyl ether solution was then cooled down to approximately 35 °C after which $CH_2Cl_2$ was added, immediately followed be cooling to prevent the Grignard reagent to react with the solvent (–55 °C). Preformed CuBr/Taniaphos (**18**) complex was added to the solution and substrate **8** was added *via* a syringe. The copper-catalyzed hetero asymmetric allylic alkylation resulted in Western part **5** in 43% yield over two steps with an ee of >98% (determined *via* the corresponding Mosher ester of the hydrolyzed allylic alcohol).

### 5.4.4 End game: towards the total synthesis of Mycoside B

Eastern part **6** and Western part **5** were coupled under cross-metathesis conditions using Hoveyda-Grubbs second generation catalyst (**20**) (Scheme 7). The reaction was slow and initially resulted in a mixture of the homo-dimer of **6** and the starting materials. The homo-dimer could still react, however, and resulted in the less reactive and desired hetero-coupled product **38** (69% yield, only the *E*-isomer was observed). Hydrolysis of **38** gave allylic alcohol **4** in 78% yield.

The Sharpless epoxidation was performed under exactly the same conditions as for test substrate **22** and led to the formation of **39** in 72% yield and the same 10:1 ratio favoring the *anti*-epoxide **39**. The diastereomers were separated by flash column chromatography. In the final step epoxide **39** was treated with 5 equivalents of Red-Al at room temperature in THF, similar conditions as were used for epoxide **23**. To our great surprise and disappointment, the reductive epoxide ring opening turned out extremely selective, favoring the undesired 1,2-diol **41**! The

observed ratio between the 1,3-diol (**40**) and 1,2-diol (**41**) was 1:10, respectively, (94% yield).




**Scheme 7:** Cross metathesis between the eastern and western part followed by Sharpless epoxidation and reductive ring opening.

The reason for this reversed selectively could be the result of a coordinating effect of the methoxy functionality in **39** (or the more distant MeOPh) which is not present in the test substrate. This seems highly unlikely, however, because there is no coordination site available on the aluminum intermediate species. Moreover the reaction is performed in THF and therefore coordination with the solvent would seem much more

likely and did not lead to selectivity problems with the test substrate. The reaction was only performed once due to the small amount of the available material. The unexpected outcome could thus be an anomaly but is difficult to explain. Alternatively, a radical epoxide ring-opening strategy with $Cp_2TiCl$ and *t*-BuSH in THF could improve the selectivity of epoxide opening as was reported for closely related epoxides.[41]

## 5.5 Conclusions

We developed a highly enantioselective and robust method for the construction of the Eastern part (olefin **6**) of Mycoside B by applying a copper/phosphoramidite-catalyzed 1,4-addition reaction on cycloheptenone with $Me_2Zn$. The formed enolate was successfully trapped with ethyl iodide leading to the formation of the *trans*-product in near perfect stereocontrol. After 6 additional steps olefin **6** was obtained in 34% overall yield (7 steps).

The western part of Mycoside B was successfully synthesized by a copper-catalyzed asymmetric allylic alkylation reaction with functionalized Grignard reagent **37**. We found that the formation of such Grignard reagents works very well at higher temperatures in *n*-butyl ether without the loss of enantioselectivity in the allylic alkylation reaction itself. Olefin **5** was obtained in 20% overall yield in 5 steps with an ee of >98%.

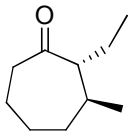
The cross metathesis of the two functionalized olefins **5** and **6** resulted in the formation of the desired benzyl ester of allylic alcohol **38**. This key step in our strategy clearly demonstrates the power of the cross-metathesis reaction in total synthesis.

After the successful Sharpless epoxidation of allylic alcohol **39** we tried selective reductive epoxide ring-opening reaction with Red-Al which failed for unclear reasons. We found that the undesired 1,2-diol was the major product. This is, however, the result of one attempt and needs further investigation. Although this strategy proved to work very well for our test substrate, it unfortunately failed in the synthesis of the more highly functionalized phenolphthiocerol. The strategy presented in this chapter did not lead to the synthesis of Mycoside B, but we did develop effective new strategies and methodologies which can be readily used in the synthesis of complex molecules.

## 5.6 Experimental

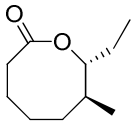
For general experimental procedures, see chapter 2, experimental section.

**(2*R*)-Ethyl-(3*S*)-methylcycloheptanone (27)**



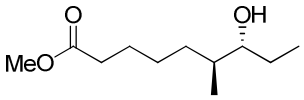
(*S*,*R*,*R*)-**25** (146 mg, 0.27 mmol, 1.0 mol%) and $Cu(OTf)_2$ (49 mg, 0.14 mmol, 0.5 mol%) were dissolved in dry toluene (60 mL) and stirred for 30 min under nitrogen at room temperature. The mixture was cooled at –25 °C and $Me_2Zn$ (1.2 M in toluene, 34 mL, 40.36 mmol, 1.5 equiv) was added dropwise over 5 min. After stirring for 10 min, a solution of cycloheptenone (3.0 mL, 26.91 mmol) in dry toluene (60 mL) was added over 5 h by syringe pump and the resulting mixture was stirred overnight at –25 °C. Ethyl iodide (22.0 mL, 269 mmol, 10.0 equiv.) and hexamethylphosphoramide (47.0 mL, 269 mmol, 10 equiv.) were added, the mixture was warmed up to 0 °C and stirred for 60 h. The reaction was quenched with aq. $NH_4Cl$ (sat.), the mixture extracted with diethyl ether, washed with brine (sat.) and dried ($Na_2SO_4$). The solvents were removed under reduced pressure and the product was purified by flash chromatography (pentane/diethyl ether, 50:1) to give **27** (3.44 g, 22.3 mmol, 83%, >95:5 *trans*:*cis*, 95% ee for *trans*) as a colorless oil. $[\alpha]_D$ = –50° (c = 4.9, $CHCl_3$). $^1$H-NMR ($CDCl_3$, 400 MHz) $\delta$ = 0.82 (t, *J* = 7.4 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H), 1.20 (m, 1H), 1.32-1.69 (m, 6H), 1.83 (m, 2H), 1.99 (td, *J* = 3.8 Hz, *J* = 10.9 Hz, 1H), 2.27 (m, 1H), 2.55 (td, *J* = 3.6 Hz, *J* = 11.8 Hz, 1H) ppm. $^{13}$C-NMR ($CDCl_3$, 100.6 MHz) $\delta$ 11.9 (q), 21.0 (q), 24.1 (t), 26.0 (t), 28.0 (t), 35.6 (d), 36.1 (t), 41.2 (t), 61.8 (d), 216.0 (s) ppm. MS (CI) for $C_{10}H_{18}O$: m/z = 172.2 $[M+NH_4]^+$, HRMS(EI) calculated for $C_{10}H_{18}O$ 154.1358, found 154.1353.

**(8*R*)-Ethyl-(7*S*)-methyloxocan-2-one (28)**



A solution of **27** (3.30 g, 21.39 mmol) in $CH_2Cl_2$ (15 mL) was added to a suspension of *m*-chloroperbenzoic acid (70-75%, 25.28 g, 106.95 mmol, 5.0 equiv.) in $CH_2Cl_2$ (15 mL) and the resulting mixture was heated at reflux for 60 h. The reaction mixture was cooled to room temperature, washed with aq. $NaHCO_3$ (sat.) and aq. $Na_2S_2O_3$ (sat.) and then dried ($Na_2SO_4$). The $CH_2Cl_2$ was removed under reduced pressure and the product was purified by flash chromatography (pentane/diethyl ether, 50:1) to give **28** (2.18 g, 12.83 mmol, 60%) as a colorless oil. $[\alpha]_D$ = –54° (c = 5.2, $CHCl_3$). $^1$H-NMR ($CDCl_3$, 400 MHz) $\delta$ = 0.85 (d, *J* = 6.9 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H), 1.28 (m, 1H), 1.41-1.92 (m, 8H), 2.38 (t, *J* = 6.4 Hz, 2H), 4.28 (td, *J* = 2.5 Hz, *J* = 9.5 Hz, 1H) ppm. $^{13}$C-NMR ($CDCl_3$, 100.6 MHz) $\delta$ 177.3 (s), 84.6 (d), 40.9 (t), 33.7 (t), 33.4 (d), 29.6 (t), 25.8 (t), 24.3 (t), 17.8 (q), 9.9 (q). MS (CI) for $C_{10}H_{18}O_2$: m/z = 188.2 $[M+NH_4]^+$, HRMS(EI) calculated for $C_{10}H_{18}O_2$-$C_2H_5$: 141.0915, found 141.0921.

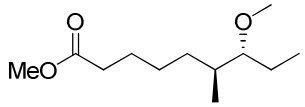
**(7*R*)-Hydroxy-(6*S*)-methylnonanoic acid methyl ester (29)**



To a solution of **28** (1.81 g, 10.63 mmol) in methanol (30 mL), activated $K_2CO_3$ (1.47 g, 10.63 mmol, 1.0 equiv.) was added and the resulting mixture was stirred for 3 h at room temperature. The reaction was quenched with aq. $NH_4Cl$ (sat.) and the methanol was removed under reduced pressure. The product was then extracted with $CH_2Cl_2$ and the solution was dried ($Na_2SO_4$). The solvent was removed under reduced pressure and the product was purified by flash chromatography (pentane/EtOAc, 9:1) to give **29** (1.94 g, 9.57 mmol, 90%) as a colorless oil. $[\alpha]_D^{22}$ = –9.9° (c = 2.8, $CHCl_3$). $^1$H-NMR ($CDCl_3$, 400 MHz) $\delta$ = 0.85 (d, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H), 1.03-1.68 (m, 9H, 1O<u>H</u>), 2.29 (t, *J* = 7.2 Hz, 2H), 3.30 (m, 1H), 3.63 (s, 3H) ppm. $^{13}$C-NMR ($CDCl_3$, 100.6 MHz) $\delta$ 174.2 (s), 77.3 (s), 51.4 (q), 38.2 (d), 34.0 (t), 31.4 (t), 26.7 (t), 26.2 (t), 25.2 (t), 15.3 (q), 10.3 (q). ppm. MS (CI) for $C_{11}H_{22}O_3$: m/z = 220.3

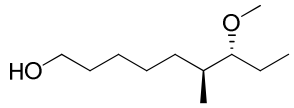
$[M+NH_4]^+$, HRMS(EI) calculated for $C_{11}H_{22}O_3$-$C_2H_5$: 173.1178, found 173.1172.

**(7*R*)-Methoxy-(6*S*)-methylnonanoic acid methyl ester (9)**




To a solution of **29** (1.00 g, 4.94 mmol) in dry DMF (30 mL), MeI (4.62 mL, 74.15 mmol, 15.0 equiv.) and NaH (60%, 1.98 g, 49.43 mmol, 10.0 equiv.) were added at 0 °C. The resulting suspension was stirred overnight under nitrogen at 40 °C, after which the reaction was quenched with $H_2O$ and the mixture extracted with diethyl ether. The combined organic layers were washed with brine (sat.), dried ($MgSO_4$) and concentrated. The product was purified by flash chromatography (pentane/EtOAc, 9:1) to give **9** (983 mg, 4.54 mmol, 92%) as a colorless oil. $[\alpha]_D$ = –3.1° (c = 2.8, $CHCl_3$). $^1$H-NMR ($CDCl_3$, 400 MHz) $\delta$ = 0.81 (d, *J* = 6.9 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H), 1.09 (m, 1H), 1.23 (m, 1H), 1.32-1.50 (m, 4H), 1.54-1.72 (m, 3H), 2.30 (t, *J* = 7.6 Hz, 2H), 2.84 (m, 1H), 3.31 (s, 3H), 3.65 (s, 3H) ppm. $^{13}$C-NMR ($CDCl_3$, 100.6 MHz) $\delta$ = 174.2 (s), 86.6 (d), 57.4 (q), 51.4 (q), 34.7 (d), 34.0 (t), 32.2 (t), 27.0 (t), 25.2 (t), 22.3 (t), 14.7 (q), 9.9 (q). ppm. MS (CI) for $C_{12}H_{24}O_3$: m/z = 234.2 $[M+NH_4]^+$, HRMS(EI) calculated for $C_{12}H_{24}O_3$-$OCH_3$ 185.1541, found 185.1540.

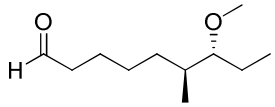
**(7*R*)-Methoxy-(6*S*)-methylnonan-1-ol (30)**




To a solution of **9** (600 mg, 2.77 mmol) in dry THF (14 mL) at –78 °C, a solution of DIBAL-H (20% in toluene, 5.0 mL, 5.82 mmol, 2.1 equiv.) was added. The resulting mixture was stirred overnight under nitrogen at –78 °C, after which the reaction was quenched with an aqueous solution of Rochelle salt and followed by extraction with $Et_2O$. The combined organic layers were washed with brine (sat.), dried ($MgSO_4$) and concentrated. The product was purified by flash chromatography (pentane/EtOAc, 9:1) to give **30** (496 mg, 2.63 mmol, 95%) as a colorless oil. $[\alpha]_D$ = –3.5° (c = 3.3, $CHCl_3$). $^1$H-NMR ($CDCl_3$, 400 MHz) $\delta$ = 0.83 (d, *J* = 6.8 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H), 1.10 (m, 1H), 1.20-1.76 (m, 10H, 1O<u>H</u>), 2.87 (m, 1H), 3.33

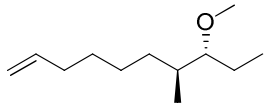
(s, 3H), 3.64 (m, 2H) ppm. $^{13}$C-NMR ($CDCl_3$, 100.6 MHz) δ 86.7 (d) 62.7 (t), 57.3 (q), 34.7 (d), 32.7 (t), 32.5 (t), 27.2 (t), 26.0 (t), 22.3 (t), 14.7 (q), 9.9 (t). MS (CI) for $C_{11}H_{24}O_2$: m/z = 206.2 $[M+NH_4]^+$, HRMS(EI) calculated for $C_{11}H_{24}O_2$-$OCH_3$ 157.1592, found 157.1589.

**(7*R*)-Methoxy-(6*S*)-methylnonanal (10)**



To a solution of **30** (545 mg, 2.89 mmol) in dry $CH_2Cl_2$ (15 mL), Dess-Martin reagent (1.35 g, 3.18 mmol, 1.1 equiv.) was added and the resulting mixture was stirred under nitrogen at room temperature for 30 min. The reaction was quenched with aq. $Na_2S_2O_3$ (sat.) and aq. $NaHCO_3$ (sat.) and then the mixture was extracted with $CH_2Cl_2$. The combined organic layers were washed with brine (sat.), dried ($MgSO_4$) and concentrated. The product was purified by flash chromatography (pentane/EtOAc, 9:1) to give **10** (494 mg, 92% yield) as a colorless oil. The product turned out to be unstable (oxidation to the acid) and was therefore immediately used in the next reaction. $[\alpha]_D$ = –5.3° (c = 3.1, $CHCl_3$). $^1$H-NMR ($CDCl_3$, 400 MHz) δ = 0.79 (d, *J* = 6.8 Hz, 3H), 0.86 (t, *J* = 7.5 Hz, 3H), 1.06 (m, 1H), 1.22 (m, 1H), 1.30-1.47 (m, 4H), 1.50-1.66 (m, 3H), 2.39 (td, *J* = 1.8 Hz, *J* = 7.3 Hz, 2H), 2.82 (m, 1H), 3.28 (s, 3H), 9.72 (t, *J* = 1.8 Hz, 1H) ppm. $^{13}$C-NMR ($CDCl_3$, 100.6 MHz) δ 202.6 (s). 86.5 (d), 57.3 (q), 43.8 (t), 34.7 (d), 32.2 (t), 27.0 (t), 22.3 (t), 14.7 (q), 9.8 (q).

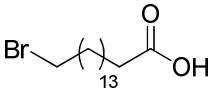
**(7*S*,8*R*)-8-Methoxy-7-methyldec-1-ene (6)**



Freshly prepared aldehyde **10** (100 mg, 0.530 mmol) was dissolved in 10 mL toluene and stirred at rt. Tebbe reagent (2.121 mL, 1.060 mmol, 0.5M in toluene) was added dropwise to the stirred solution over 10 min. The reaction was followed by TLC ($CH_2Cl_2$) until the reaction was completed (15 min). After quenching with 10 mL of saturated aq. $NH_4Cl$ solution, 10 mL of diethyl ether was added. The phases were separated and the aqueous layer was extracted with three portions of 10 mL diethyl ether. The combined organic phases were dried over $MgSO_4$ and concentrated

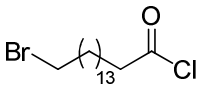
under reduced pressure to yield crude **6**, which was purified by flash chromatography ($CH_2Cl_2$) to afford **6** as a colorless oil (87 mg, 89% yield (two steps), $[\alpha]_D$ = –1.0° (c = 1.5, $CHCl_3$)). $^1$H-NMR ($CDCl_3$, 400 MHz) δ 5.81 (m, 1H), 4.96 (m, 2H), 3.34 (s, 3H), 2.87 (m, 1H), 2.06 (m, 2H), 1.68 (m, 1H), 1.50-1.02 (br, 9H), 0.91 (t, *J* = 6.9 Hz, 3H) 0.83 (d, *J* = 6.8 Hz, 3H). $^{13}$C-NMR ($CDCl_3$, 100.6 MHz) δ 139.07 (d), 114.15 (t), 86.70 (d), 57.33 (q), 34.77 (d), 34.13 (t), 33.79 (t), 32.50 (t), 29.26 (t), 27.02 (t), 14.71 (q), 10.08 (q). HRMS(ESI+) calculated for $C_{12}H_{25}O^+$ (M + $H^+$), 185.1900, found 185.1897.

**16-Bromohexadecanoic acid (33)**




To a solution of 16-hydroxyhexadecanoic acid (1.00 g, 3.67 mmol) in $CH_2Cl_2$ (20 mL) cooled to 0 °C, $PPh_3$ (2.90 g, 11.01 mmol, 3.0 equiv.) and NBS (1.63 g, 9.18 mmol, 2.5 equiv.) were added. The resulting solution was stirred under nitrogen at 0 °C for 10 min and then warmed to room temperature over 2 h. The reaction mixture was quenched with aq. $NaHCO_3$ (sat.) and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were washed with aq. $Na_2S_2O_3$ (10% v/v) and brine (sat.), dried ($MgSO_4$), filtered and concentrated. The resulting crude was purified by flash chromatography (pentane/EtOAc, 9:1) to give **33** (935 mg, 76% yield) as a white solid, mp = 67-68 °C. $^1$H-NMR ($CDCl_3$, 400 MHz) δ = 1.22-1.35 (m, 20H), 1.41 (m, 2H), 1.62 (m, 2H), 1.85 (qt, *J* = 6.9 Hz, 2H), 2.34 (t, *J* = 7.5 Hz, 2H), 3.40 (t, *J* = 6.9 Hz, 2H) ppm. $^{13}$C-NMR ($CDCl_3$, 100.6 MHz) δ 180.4 (s), 34.1 (t), 32.8 (t), 29.6 (t), 29.5 (t), 29.4 (t), 29.2 (t), 29.0 (t), 28.8 (t), 28.2 (t), 24.6 (t). ppm. MS (EI) for $C_{16}H_{31}BrO_2$: m/z = 333.8 $[M]^+$, 335.9 $[M+2]^+$, HRMS(EI) calculated for $C_{16}H_{31}BrO_2$ 334.1507, found 334.1504.

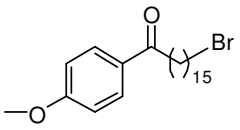
**16-Bromohexadecanoyl chloride (34)**




To a solution of **33** (930 mg, 2.77 mmol) in $CH_2Cl_2$ (20 mL) cooled at 0 °C, oxalyl chloride (0.5 mL, 5.54 mmol, 2.0 equiv.) was added. The resulting

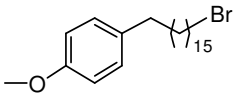
mixture was stirred under nitrogen at 0 °C for 10 min and then warmed to room temperature overnight. The solvent was removed under vacuum to give **34** (833 mg, 2.35 mmol, 85%) as a yellowish oil, that was used in the next transformation without further purification. $^1$H-NMR ($CDCl_3$, 400 MHz) $\delta$ = 1.21-1.34 (m, 20H), 1.42 (m, 2H), 1.71 (m, 2H), 1.85 (dt, *J* = 6.9 Hz, 2H), 2.88 (t, *J* = 7.3 Hz, 2H), 3.41 (t, *J* = 6.9 Hz, 2H) ppm.

**16-Bromo-1-(4-methoxyphenyl)-hexadecan-1-one (35)**




To a solution of **34** (833 mg, 2.35 mmol) in $CH_2Cl_2$ (20 mL) cooled to 0 °C, $AlCl_3$ (470 mg, 3.53 mmol, 1.5 equiv.) was added, followed by anisole (1.3 mL, 11.75 mmol, 5.0 equiv.). The resulting solution was stirred under nitrogen at 0 °C for 10 min and then warmed to room temperature overnight. The reaction mixture was quenched by pouring it into a separation funnel containing ice. After 30 min the organic layer was collected, washed with water until the aqueous extract was neutral, dried ($MgSO_4$), filtered and concentrated. The resulting crude product was purified by flash chromatography (pentane/diethyl ether, 9:1) to give **35** (820 mg, 82% yield) as a white solid. mp = 65-66 °C. $^1$H-NMR ($CDCl_3$, 400 MHz) $\delta$ = 1.15-1.67 (m, 22H), 1.71 (m, 2H), 1.84 (qt, *J* = 6.9 Hz, 2H), 2.90 (t, *J* = 7.3 Hz, 2H), 3.39 (t, *J* = 6.9 Hz, 2H), 3.86 (s, 3H), 6.92 (d, *J* = 9.0 Hz, 2H), 7.93 (d, *J* = 9.0 Hz, 2H) ppm. $^{13}$C-NMR ($CDCl_3$, 100.6 MHz) $\delta$ 199.2 (s), 163.2 (s), 130.3 (d), 113.6 (d), 55.4 (q), 38.3 (t), 34.0 (t), 32.8 (t), 29.6 (t), 29.5 (t), 29.4 (t), 28.7 (t), 28.2 (t), 24.6 (t). ppm. MS (EI) for $C_{23}H_{37}BrO_2$: m/z = 424.0 $[M]^+$, 426.0 $[M+2]^+$, HRMS(EI) calculated for $C_{23}H_{37}BrO_2$ 424.1977, found 424.1968.

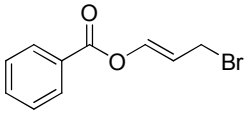
**1-(16-Bromohexadecyl)-4-methoxybenzene (36)**




A sample of zinc + mercury amalgam was freshly prepared by suspending Zn powder (853 mg, 13.05 mmol, 15.0 equiv.) and $HgCl_2$ (119 mg, 0.87

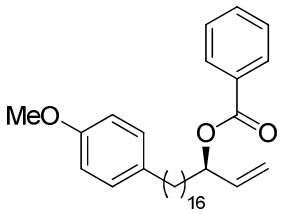
mmol, 1.0 equiv.) in a mixture of water (4.0 mL) and 12 M aq. HCl (2.5 mL). After stirring the resulting suspension for 10 min, a solution of **35** (370 mg, 0.87 mmol) in toluene (5.5 mL) was added. The resulting two-phase mixture was heated and stirred vigorously such that both phases were in frequent contact with the amalgam. After 16 h under reflux, during which two 0.5 mL portions of 12 M aq. HCl were added, the reaction flask was allowed to cool to room temperature and the organic phase was collected, washed with water and dried ($MgSO_4$). The resulting solution was concentrated and purified by flash chromatography (pentane/diethyl ether, 95:5) to give **36** (315 mg, 0.77 mmol, 88%) as a white solid, mp = 33-34 °C. $^1$H-NMR ($CDCl_3$, 400 MHz) δ 1.17-1.37 (m, 22H), 1.44 (m, 2H), 1.59 (m, 2H), 1.87 (qt, *J* = 6.9 Hz, 2H), 2.56 (t, *J* = 7.6 Hz, 2H), 3.42 (t, *J* = 6.9 Hz, 2H), 3.80 (s, 3H), 6.83 (d, *J* = 8.6 Hz, 2H), 7.10 (d, *J* = 8.6 Hz, 2H). $^{13}$C-NMR ($CDCl_3$, 100.6 MHz) δ 157.5 (s), 135.0 (s), 129.2 (d), 113.6 (d), 55.2 (q), 35.0 (t), 34.0 (t), 32.8 (t), 31.8 (t), 29.7 (t), 29.6 (t), 29.5 (t), 29.4 (t), 29.3 (t), 28.8 (t), 28.2 (t). MS (EI) for $C_{23}H_{39}BrO$: m/z = 410.2 $[M]^+$, 412.2 $[M+2]^+$, HRMS(EI) calculated for $C_{23}H_{39}BrO$ 410.2184, found 410.2166.

**(*E*)-3-Bromoprop-1-enyl benzoate (8)**




Freshly distilled acrolein (2.8 mL, 41.96 mmol) was dissolved in $CH_2Cl_2$ (40 mL) at 0 °C and benzoyl bromide (5.0 mL, 41.96 mmol, 1.0 equiv.) was added. The resulting solution was allowed to warm to room temperature and stirred for 72 h. The reaction was quenched by addition of aq. $NaHCO_3$. The aqueous layer was extracted with $CH_2Cl_2$ and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. The resulting crude was purified by recrystallization from pentane to give the pure *E* isomer **8** (5.76 g, mmol, 57%) as a white solid.[26]

**(*R*)-19-(4-Methoxyphenyl)nonadec-1-en-3-yl benzoate (5)**

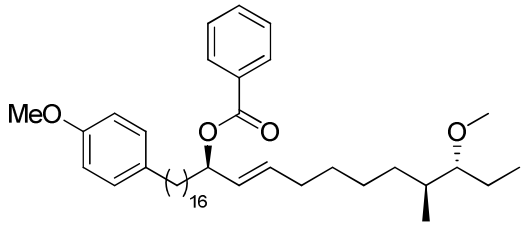



First a solution of the corresponding Grignard reagent of **36** was prepared in *n*-butyl ether at 100 °C for 5 h (550 mg, 1.335 mmol **34** together with 36 mg, 1.481 mmol Mg(s) in 5 mL *n*-butyl ether). The solution was cooled to 35 °C, 20 mL $CH_2Cl_2$ was added and the mixture was stirred vigorously for 1 min after which it was quickly cooled down to –55 °C. A second portion of 20 mL of $CH_2Cl_2$ was added and stirring was continued for 15 min. A pre-stirred (10 min) solution of (–)-($S,S_{Fe}$)-Taniaphos (21.3 mg, 0.031 mmol) and CuBr•$SMe_2$ (5.1 mg, 0.025 mmol) in 2 mL of $CH_2Cl_2$ was added and the suspension was stirred for 10 min. Substrate **8** (322 mg, 1.335 mmol) was added dropwise in $CH_2Cl_2$ (3 mL) over 15 min. The reaction mixture was quenched with 3 mL MeOH after 16 h at –55 °C. A saturated aq. $NH_4Cl$ solution (50 mL) was added, together with 50 mL ether and the mixture was brought to rt and stirred for 30 min. The layers were separated and the water layer was extracted with 2 additional portions of 20 mL ether. The organic layers were combined, dried on $MgSO_4$ and concentrated under reduced pressure and purified by flash chromatography (pentane/diethyl ether, 50:1) to afford **5** as a colorless oil (282 mg, 43% yield).$^1$H-NMR (400 MHz) δ 8.07 (dd, *J* = 1.3, 8.4 Hz, 2H), 7.56 (m, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.90 (m, 1H), 5.49 (m, 1H), 5.26 (m, 2H), 3.79 (s, 3H), 2.54 (m, 2H), 1.75 (m, 2H), 1.57 (m, 2H), 1.45-1.20 (m, 26H). An analytical sample of compound **5** was hydrolyzed with KOH in a mixture of EtOH/THF/$H_2O$ to the give allylic alcohol which was used to determine the ee *via* the Mosher ester (ee >98%). Spectral data allylic alcohol $^1$H-NMR ($CDCl_3$, 400 MHz) δ 7.09 (d, *J* = 7.3 Hz, 2H), 6.82 (dd, *J* = 1.2, 8.3 Hz, 2H), 5.87 (m, 1H) ppm 5.16 (ddd, *J* = 13.8, 11.4, 1.1 Hz, 2H), 4.09 (m, 1H), 3.78 (s, 3H) 2.53 (t, *J* = 7.6 Hz, 2H) ppm 1.60-1.20 (br, 31H). $^{13}$C-NMR ($CDCl_3$, 100.6 MHz) δ 157.50 (s), 141.31 (d), 134.99 (s), 129.20 (d), 114.50 (t), 113.60 (d), 73.27 (d), 55.23 (q), 37.04 (t), 35.02 (t), 31.75 (t), 29.73 (t), 29.66 (t, 8 x C), 29.59

(t), 29.54 (t), 29.27 (t), 25.32 (t). HRMS(ESI+) calculated for $C_{36}H_{62}O_2^+$ (M – $H_2O$) 371.3308, found 371.3294.

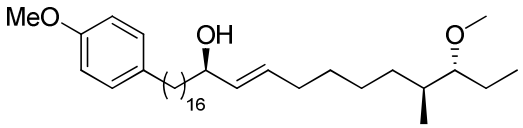
The spectral data of the Mosher ester from *S*-(+)-Mosher acid chloride and the allylic alcohol. $^1$H-NMR ($CDCl_3$, 400 MHz) δ 5.81 (m) for $CH_2C$(O-Mosher)C<u>H</u>=$CH_2$. Diastereomers from the product of racemic allylic alcohol with *S*-(+)-Mosher acid chloride; $^1$H-NMR ($CDCl_3$, 400 MHz) δ 5.81 (m) and 5.71 (m) for $CH_2C(O)C\underline{H}=CH_2$. (ester formation with *S*-(+)-Mosher acid chloride results in the *R*-Mosher ester!).

**(3*R*,4*S*,11*R*,*E*)-3-Methoxy-27-(4-methoxyphenyl)-4-methylheptacos-9-en-11-yl benzoate (38)**



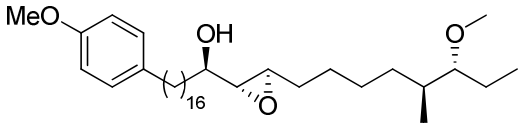

Compound **5** (83 mg, 0.169 mmol) was dissolved in dry $CH_2Cl_2$ (0.5 mL) previously degassed for 30 min by a nitrogen flow and then **6** (47 mg, 0.253 mmol, 1.5 equiv., in 0.2 mL) was added. HG-2 catalyst (2.6 mg, 2.5 mol%) was added and the resulting mixture was refluxed for 3 h. Another portion of HG-2 catalyst (2.6 mg, 2.5 mol%) was added and the resulting suspension was heated at reflux overnight. The reaction mixture was cooled to room temperature and the solvent removed under vacuum. The resulting crude was purified by flash chromatography ($CH_2Cl_2$) to give **38** (76 mg, 69% yield, $[\alpha]_D$ = –12.3° (*c* = 1.14, $CHCl_3$) as a pure *E* isomer). $^1$H-NMR (400 MHz) δ 8.05 (d, *J* = 7.1 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 5.78 (m, 1H), 5.47 (m, 2H), 3.79 (s, 3H), 3.32 (s, 3H), 2.85 (m, 1H), 2.54 (m, 2H), 2.05 (m, 2H), 1.78 (m, 1H), 1.67 (m, 2H), 1.56 (m, 2H), 1.50-1.00 (br, 34H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H). $^{13}$C-NMR ($CDCl_3$, 100.6 MHz) δ 165.86 (s), 157.52 (s), 135.01 (s), 134.36 (d), 132.62 (d), 130.87 (s), 129.50 (d), 129.18 (d), 128.40 (d), 128.21 (d), 113.57 (d), 86.62 (d), 75.61 (d), 57.33 (q), 55.19 (q), 35.01 (t), 34.74 (d), 34.67(t), 32.40 (t), 32.17 (t), 31.73 (t), 29.65 (t, 5 x C), 29.61 (t), 29.58 (t), 29.56 (t), 29.50 (t, 2 x C), 29.39 (t), 29.25 (t), 29.22 (t), 26.93 (t), 25.22 (t), 22.31 (t), 14.68 (q), 10.07 (q). HRMS(ESI+) calculated for $C_{43}H_{68}O_4$ 671.5015, found 671.5005.

**(3*R*,4*S*,11*R*,*E*)-3-Methoxy-27-(4-methoxyphenyl)-4-methylheptacos-9-en-11-ol (4)**




Benzoyl ester **38** (78 mg, 0.120 mmol) was dissolved in a mixture of MeOH, THF and $H_2O$ (1:1:1, 5 mL) and 10 eq. KOH (67 mg, 1.20 mmol) was added. The mixture was stirred for 17 h at rt. Diethyl ether was added (10 mL) together with 5 mL $H_2O$. After phase separation and extraction of the aqueous phase with 3 portions of diethyl ether (10 mL), the combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (pentane/diethyl ether, 1:1) to afford **4** as a white solid (51 mg, 78% yield). $^1$H-NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.62 (td, *J* = 6.7, 15.3 Hz, 1H), 5.45 (dd, *J* = 7.1, 15.3 Hz, 1H), 4.03 (m, 1H), 3.78 (s, 3H), 3.34 (s, 3H), 2.87 (m, 1H), 2.54 (m, 2H), 2.02 (m, 2H), 1.67 (m, 2H), 1.52-0.92 (br, 38H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H). $^{13}$C-NMR ($CDCl_3$, 100.6 MHz) δ 157.50 (s), 134.99 (s), 133.11 (d), 131.93 (d), 129.16 (d), 113.56 (d), 86.66 (d), 73.13 (d), 57.33 (q), 55.16 (q), 37.32 (t), 34.99 (t), 34.76 (d), 32.39 (t), 32.13 (t), 31.72 (t), 29.64 (t, 7 x C), 29.58 (t, 2 x C), 29.55 (t), 29.49 (t), 29.44 (t), 29.24 (t), 26.99 (t), 25.47 (t), 22.32 (t), 14.75 (q), 10.04 (q). HRMS(ESI+) calculated for $C_{36}H_{64}O_3$ (M + $Na^+$) 567.4753, found 567.4738.

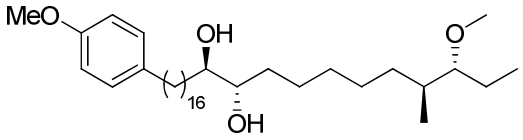
**(*R*)-1-((2*R*,3*R*)-3-((5*S*,6*R*)-6-Methoxy-5-methyloctyl)oxiran-2-yl)-17-(4-methoxyphenyl)heptadecan-1-ol (39)**




Ti(*i*-PrO)$_4$ (28 μL, 0.092 mmol, 1 equiv.) and (–)-*D*-diethyl tartrate (19 μL, 0.110 mmol, 1.2 equiv.) were dissolved in $CH_2Cl_2$ (1 mL) containing activated molecular sieves. The resulting mixture was stirred for 5 min at room temperature and then a solution of **4** (50 mg, 0.092 mmol) in $CH_2Cl_2$

(1.5 mL) was added. After stirring the resulting mixture for 30 min, t-butylhydroperoxide 5.0-6.0 M in decane (37 μL, 0.184 mmol, 2.0 equiv.) was added and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with an aqueous solution of *D*,*L*-tartaric acid (10%) and the two layers obtained were separated. The aqueous layer was extracted with $CH_2Cl_2$ and the combined organic layers were dried ($Na_2SO_4$). The solvents were removed under reduced pressure and the crude was purified by flash chromatography (pentane/diethyl ether, 1:1) to give **39** (37 mg, 0.151 mmol, 72%). $^1$H-NMR (400 MHz) δ 7.09 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 3.78 (s, 3H), 3.78 (m, 1H), 3.33 (s, 3H), 2.99 (m, 1H), 2.86 (m, 1H), 2.76 (m, 1H), 2.53 (m, 2H), 1.70-1.10 (br, 42H), 0.91 (t, *J* = 7.3 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H). $^{13}$C-NMR ($CDCl_3$, 100.6 MHz) δ 157.50 (s), 135.06 (s), 129.21 (d), 113.61 (d), 86.66 (d), 68.50 (d), 60.96 (d), 57.40 (q), 55.24 (q), 54.90 (d), 35.03 (t), 34.81 (d), 33.55 (t), 32.51 (t), 31.76 (t), 31.63 (t), 29.68 (t, 8 x C), 29.60 (t), 29.55 (t), 29.52 (t), 29.28 (t), 27.33 (t), 26.40 (t), 25.34 (t), 22.37 (t), 14.84 (q), 10.02 (q).

**(3*R*,4*S*,10*S*,11*R*)-3-Methoxy-27-(4-methoxyphenyl)-4-methylheptacosane-10,11-diol (41)**




Red-Al 3.5 M in toluene (51 μL, 0.178 mmol, 5.0 equiv.) was added to a solution of **39** (20 mg, 0.036 mmol) in THF (2 mL) and the resulting mixture was stirred at room temperature for 24 h. The reaction was quenched with an aqueous solution of Rochelle salt and the mixture extracted with diethyl ether. The combined organic layers were dried ($MgSO_4$) and concentrated. The product was purified by flash chromatography (pentane/diethyl ether, 1:1) to give a mixture of diols **40** and **41** in a 1:10 ratio (19 mg, 94%) as a white solid. $^1$H-NMR (400 MHz) δ 7.09 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 3.78 (s, 3H), 3.60 (m, 2H), 3.33 (s, 3H), 2.87 (ddd, *J* = 4.1, 5.2, 7.5 Hz, 1H), 2.53 (m, 2H), 1.90 (m, 2H), 1.72-1.00 (br, 43H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H). 1,3-diol chemical shift (C<u>H</u>OH) multiplet δ 3.94, 1,2-diol chemical shift (C<u>H</u>OH) multiplet δ 3.60. $^{13}$C-NMR ($CDCl_3$, 100.6 MHz) δ 157.52 (s),

135.03 (s), 129.19 (d), 113.59 (d), 86.69 (d), 74.66 (d), 74.60 (d), 57.35 (q), 55.21 (q), 35.01 (d), 34.77 (d), 32.59 (d), 32.56 (d), 31.90 (d), 31.74 (d), 31.21 (d), 31.15 (d), 29.95 (d), 29.90 (d), 29.66 (d, 4 x C), 29.58 (d, 2 x C), 29.50 (d), 29.26 (d), 27.44 (d), 26.00 (d), 25.96 (d), 22.67 (d), 22.32 (d), 14.75 (q), 10.06 (q). HRMS(ESI+) calculated for $C_{36}H_{66}O_4$ ($M + Na^+$) 585.4859, found 585.4825.

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